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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,119	05/16/2006	Charles R Cantor	701586-054202US	7233

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Ronald I Eisenstein
Nixon Peabody
100 Summer Street
Boston, MA 02110-2131

EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,119	CANTOR ET AL.	
	Examiner	Art Unit	
	MISOOK YU	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/10/08, 3/23/07, 11/30/06, 5/16/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of group 1 in the reply filed on 02/26/2008 is acknowledged.

Claims 1-17 are pending and examined on merits.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 16 and17 are rejected under 35 U.S.C. 102(2) as being anticipated by US-PAT-NO: 6,927,028 (filing date of 08/31/2001)

Claims 16 and 17 are drawn to a method of diagnosing fetal chromosomal abnormality comprising the steps of: a) obtaining a plasma sample from a pregnant female; b) selectively treating said plasma sample to enrich the sample for at least one fetal nucleic acid region; c) determining the paternal or maternal allele frequency using at least one polymorphic marker adjacent to or within the at least one fetal nucleic acid region in the sample of step (b); and d) comparing the paternal or maternal allele frequency of step (c) to a control DNA sample, wherein a difference in allele frequency

from other than 50% of paternal and 50% of maternal allele is indicative of a chromosomal abnormality.

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In a second aspect, the present invention features methods of detecting abnormalities in a fetus by detecting fetal DNA in a biological sample obtained from a mother. The methods according to the present invention provide for detecting fetal DNA in a maternal sample by differentiating the fetal DNA from the maternal DNA based upon epigenetic markers such as differences in DNA methylation. Employing such methods, fetal DNA that is predictive of a genetic anomaly or genetically based disease may be identified thereby providing methods for prenatal diagnosis. These methods are applicable to any and all pregnancy-associated conditions for which methylation changes associated with a disease state is identified. Exemplary diseases that may be diagnosed include, for example, preeclampsia, a chromosomal aneuploidy, including but not limited to trisomy 21, Prader-Willi Syndrome, and Angelman Syndrome

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The present invention allows detecting or predicting the presence of any disorders of the fetus or the mother which are associated with a change in methylation status of a DNA sequence. Examples include imprinting disorders such as Prader-Willi syndrome (Kubota et al., Nat Genet 16(1):16-7 (1997). The present invention provides a new type of test for preeclampsia which has been suggested to be an imprinting disorder (Graves, Reprod Fertil Dev 10(1):23-9 (1998). The present invention further provides a new type of test for chromosomal aneuploidies, including Down syndrome (trisomy 21), which may be associated with methylation changes (Yu et al., Proc Natl Acad Sci USA 94(13):6862-7 (1997).

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In a fourth aspect, the present invention features kits for differentiating DNA species originating from different individuals in a biological sample. Such kits are useful, for instance, for differentiating or detecting the presence of fetal DNA in a maternal biological sample or for differentiating DNA from an organ donor or potential organ donor from that of an organ recipient or potential organ recipient. The kits according to the present invention comprise one or more reagents for ascertaining the methylation status of the maternal DNA such as sodium bisulfite and one or more reagents for detecting the presence of DNA such as a gel. Additionally, such kits may include one or more reagents for amplifying the amount of DNA present in the sample such as one or more reagents for performing polymerase chain reaction amplification. Such reagents are well known to those of skill in the art. Further, such kits may include one or more apparatuses for obtaining a maternal DNA sample. Such apparatuses are well known to those skilled in the art. In particular the kits according to the present invention may be used for diagnosing a disease

> caused all or in part by a genetic anomaly such as a mutation, substitution or deletion or duplication in all or part of a DNA sequence present in a fetus. Exemplary diseases that may be diagnosed include, for example, preeclampsia, a chromosomal aneuploidy, including but not limited to trisomy 21, Prader-Willi Syndrome and Angelman Syndrome

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over US-PAT-NO: 6927028 as applied to claims 16 and 17 above, and further in view of US-PAT-NO: 7348139.

Claims 1-15 are drawn to method for prenatal diagnosis of chromosomal abnormality using maternal serum or plasma as the source of DNA, the method comprising detecting differential DNA methylation between fetus and mother, wherein the differential methylation is detected using a methyl-sensitive enzyme that digests only unmethylated DNA.

US-PAT-NO: 6927028 teaches fetal epigenetic markers (i.e. differential in differential DNA methylation between fetus and mother) can be detected using the art-known method involving sodium bisulfite and a methylation-specific polymerase chain reaction. Note claims 1, 2, 9, 11, 12, 23, 24, 31 in addition to the paragraphs 9, 15, and 18 quoted above.

US-PAT-NO: 6927028 does not teach a methyl-sensitive enzyme that digests only unmethylated DNA.

However, US-PAT-NO: 7348139 (date filed on April 15, 2002) teaches the following:

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Methylation of a CpG dinucleotide in a CpG island of a SOCS/CIS gene can be detected using any of various well known methods for detecting CpG methylation of a nucleic acid molecule. For example, such methylation can be detected by contacting a nucleic acid molecule, which includes all or a portion of a CpG island of the SOCS/CIS gene sequence, with a methylation sensitive restriction endonuclease. The methylation sensitive restriction endonuclease can be one that cleaves a recognition site containing a methylated cytosine residue of a CpG dinucleotide in the SOCS/CIS gene sequence, for example, a restriction endonuclease such as Acc III, Ban I, BstN I, Msp I, or Xma I, whereby cleavage of the nucleic acid molecule indicates that the SOCS/CIS gene in the test cell is methylated. Conversely, the methylation sensitive restriction endonuclease can be one that cleaves a recognition site containing a CpG dinucleotide in the SOCS/CIS gene sequence only when the cytosine residue of the CpG dinucleotide is unmethylated, for example, a restriction endonuclease such as Acc II, Ava I, BssH II, BstU I, Hpa II, or Not I, whereby a lack of cleavage of the nucleic acid molecule indicates that SOCS/CIS gene in the test cell is methylated.

Therefore, it would have been obvious to one of ordinary skill in the art to arrive the claimed invention with a reasonable expectation of success because a methyl-sensitive enzyme that digests only unmethylated DNA had been known before the effective filing date of the claimed invention. One of ordinary skill in the art would have been motivated to use the claimed invention since using a methyl-sensitive enzyme that digests only unmethylated DNA seems to be an art-equivalent method of detecting methylation status of DNA.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MISOOK YU
Primary Examiner
Art Unit 1642

/MISOOK YU/
Primary Examiner, Art Unit 1642